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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/846,658
Filing Date: May 01, 1997
Appellant(s): ADAIR ET AL.

DOREEN YATKO TRUJILLO
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on September 08, 2006 appealing from the Office actions mailed on August 24, 2006 and May 02, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

An Appeal Brief was filed on July 17, 2006 for Application Serial No: 08/485,686, filed on June 07, 1995, which claims priority to the same applications as the present application, i.e., Application Serial Nos. 08/303,565, filed on 07/743,329, and GB Application No. 8928874, filed on 12/21/1989.

It is noted that the parent GB Application No. is 8928874, and is not GB Application No. 8938874, as cited by Appellant on page 4 of the brief.

(3) Status of Claims

The statement of the status of claims contained in the brief is substantially correct. Claims 24-31 are pending and are on appeal.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,585,089	Queen et al	12/17/1996
6,548,640B1	Winter et al	04/15/2003

Lohmeyer et al. "T-cell prolymphocytic leukemia (T-PLL) with unique surface phenotype". Blut, vol 54, no. 4 (1987), pp. 223-229.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24-31 are rejected under 35 U.S.C. 102(e) as anticipated by Queen et al (US 5,585,089), which claims as priority, SN=07/290,975, filed on 12/28/1988, and SN= 07/310,252, filed 02/13/1989, or in the alternative, as being obvious over Queen et al (US 5,585,089), and as evidenced by Winter et al (US 6,548,640B1) and Lohmeyer J et al, 1987, Blut, 54(4): 223-9.

Claims 24, 26, 28-29 are drawn to:

A humanized immunoglobulin comprising amino acids from the donor immunoglobulin framework "outside both" the Kabat CDRs and the structural loop CDRs of the variable regions, wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain framework, and each of said donor amino acids contributes

to antigen binding as determined by X-ray crystallography, and wherein the humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least $10^8\ M^{-1}$ (claim 24), or in the range 10^8-$10^{12}\ M^{-1}$ (claim 26), or with an effective antigen binding affinity (claim 28), or with an affinity similar to that of the donor immunoglobulin (claim 29).

Claims 26-27 are drawn to:

A humanized antibody of claim 24, wherein the antigen is an IL-2 receptor (claim 26), or wherein the donor immunoglobulin is the anti-CD4 T-cell receptor antibody (claim 27).

Claims 30-31 are drawn to:

A humanized antibody of claim 28, wherein the antigen is a human CD3 T-cell receptor (claim 30), or wherein the donor immunoglobulin is the anti-CD3 T-cell receptor antibody (claim 31).

Queen et al (US 5,585,089) teach:

A humanized immunoglobulin having complementarity determining regions (**CDRs**) from a donor immunoglobulin and heavy and light chain variable region frameworks from acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10.sup.7 M.sup.-1 and no greater than about four-fold that of the donor immunoglobulin, **wherein said humanized immunoglobulin comprises amino acids** from the donor immunoglobulin framework **outside the Kabat and Chothia CDRs** that replace the corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, wherein each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with amino acids in the CDRs, or

(III) is typical at its position for human immunoglobulin sequences, and the replaced amino acid in the acceptor is rare at its position for human immunoglobulin sequences (claim 4).

Further, in the prior application 07/290,975, filed on 12/28/1988, **Queen et al teach** that the variable regions of each light/heavy chain pair form the antibody binding site and that the chains all exhibit the same general structure of relatively conserved framework regions joined by three **"hypervariable regions", "also called CDR's"** (see Kabat et al, 1983 **and** Chothia et al, 1987, which are **incorporated herein by reference** (emphasis added) (Queen et al, 07/290,975, p.8, last paragraph, bridging p.9, lines 1-5).

The following is the analysis of the limitations in claim 4 of Queen et al and those in the instant claims 24-31.

A. The limitation "a humanized immunoglobulin **comprising** amino acids from the donor immunoglobulin framework "**outside both**" the Kabat CDRs and the structural loop CDRs of the variable regions" of the instant claims 24-31

In particular, Queen et al teach a humanized antibody, wherein several of the replacing donor amino acids in the framework, as shown in the specific example of a humanized anti-Tac immunoglobulin in the prior application 07/290,975, filed on 12/28/1988, are inherently **outside of both** the CDRs regions taught by Kabat and the hypervariable regions, "also called CDRs", taught by Chothia.

More specifically, Queen et al teach that the amino acids of the acceptor framework, that belong the following three categories, are replaced with the corresponding donor amino acids:

1) The amino acid of the human acceptor framework region which is **rare** is replaced with the donor amino acid (Queen et al, , 07/290,975, p. 21, item 2, lines 23-27, and 07/310,252, filed 02/13/1989, p.4, lines 7-15). In the specific example of anti-Tac immunoglobulin where the CDRs is as defined by Kabat, Queen et al teach that the replaced rare amino acids in the heavy chain are amino acids 27, 93, 95, 98, 107-109, 111 (Queen et al, 07/290,975, p. 21, item 2, lines 23-27, and Queen et al, 08/310,252, p.21, item 2, lines 23-26).

It is clear that the replaced rare amino **acids 93, 107-109, 111** in the framework of the anti-Tac immunoglobulin, as taught by Queen et al, 07/290,975, are **outside of both** the Kabat CDRs (amino acids 31-35) and the structural loop CDRs (amino acids 26-32) taught by Chothia et al .

2) The human acceptor framework amino acid, which is **immediately adjacent to one of the CDR's,** is replaced with the donor amino acid (Queen et al, 07/290,975, p.21, item 3, lines 28-30). Queen et al teach that said amino acids may make contacts with the antigen, that contribute to affinity; however said contacts are lost when all the framework amino acids are from human acceptor (Queen et al, 07/310,252, p.10, item 2, lines 20-25, p.12, criterion III, lines 17-28). In the specific example of the anti-Tac immunoglobulin, where the CDRs is as defined by Kabat, the framework amino acids that are immediately adjacent to one of the CDRs are amino acids 30 and 67 (Queen et al, 07/290,975, p.21, item 3, lines 28-30).

It is clear that the replaced **amino acid 67,** which is immediately adjacent to one of the CDR's and is in the framework of the anti-Tac immunoglobulin, as taught by Queen et al, 07/290,975, is **outside of both** the Kabat CDRs (amino acids 31-35) and the structural loop CDRs (amino acids 26-32), taught by Chothia.

3) The human acceptor framework amino acid, which is **physically close to the antigen binding region**, as suggested by 3-dimensional modeling, is replaced with the donor amino acid (Queen et al, 07/290,975, p.21, item 4, lines 31-34, Queen et al, 08/310,252, p.10, item 1, lines 11-19, p.12, criterion IV, lines 30-37, bridging p.13). Queen et al teach that these acceptor framework human amino acids that are close to the CDR's can slightly distort the CDR's, because they create different electrostatic or hydrophobic forces (hydrogen bonding, Van-der Waals forces, hydrophobic interactions etc..) than in the donor mouse antibody, and the distorted CDR's may not make as effective contacts with the antigen as the CDR's in the donor antibody (Queen et al, 07/310,252, p.10, item 1, lines 11-19, p.12, criterion IV, lines 30-37, bridging p.13). In the specific example of anti-Tac immunoglobulin, where the CDRs is as defined by Kabat, Queen et al teach that the replaced amino acids in the heavy chain that are close to the CDR's are amino acids 48 and 68 (Queen et al, 07/290,975, p.21, item 4, lines 31-34)

It is clear that the replaced **amino acids 48, 68,** which are physically close to the antigen binding region, as suggested by 3-dimensional modeling and are in the framework of the anti-Tac immunoglobulin, as taught by Queen et al, 07/290,975, are **outside of both** the Kabat CDRs (amino acids 31-35) and the structural loop CDRs (amino acids 26-32) taught by Chothia et al.

In summary, many of the replacing donor amino acids in the framework of a humanized immunoglobulin, as taught by Queen et al, that belong to at least one of the following three categories: (I) adjacent to a CDR in the donor immunoglobulin sequence, or (II) capable of interacting with amino acids in the CDRs, or (III) rare at its position for human immunoglobulin sequences (three categories in Queen et al, 07/310252, p. 10-13, and claim 4 of Queen et al, US 5,585,089), are "inherently" outside of both the CDRs as described by Kabat, "and" the

structural loop CDRs as described by Chothia et al, wherein CDRs as described by Kabat and Chothia are known in the art, as incorporated in reference by Queen et al.

In other words, **the limitation of** "a humanized immunoglobulin **comprises** amino acids from the donor immunoglobulin framework **outside the Kabat and Chothia CDRs,** that replace the corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, wherein each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with amino acids in the CDRs, or

(III) is typical at its position for human immunoglobulin sequences, and the replaced amino acid in the acceptor is rare at its position for human immunoglobulin sequences" as taught **in claim 4** in Queen et al, US 5,585,089, clearly has support, i.e. **is described,** in the prior applications of Queen et al, 07/290,975 and 07/310252.

It is noted that the description of Kabat and Chothia CDRs is **incorporated by reference by Queen et al** (Queen et al, 07/290,975, p.8, last paragraph, bridging p.9, lines 1-5). Further, the first hypervariable region, also called CDR1, as described by Kabat (i.e., amino acids 31-35), and Chothia (i.e., amino acids 26-32, or the first **structural loop**) is known in the art, as evidenced by Winter et al (US 6,548,640B1). Winter et al (US 6,548,640B1) teach as follows:

a) the first heavy chain hypervariable loop (CDR1) as taught by Kabat, (which is the same as the first hypervariable loop by sequence) extends from amino acids 31-35, and the first heavy chain CDR1 as taught by Chothia (which is the same as the first hypervariable loop by structure) extends from amino acids 26 to 32 (Winter et al, US 6,548,640B1, column 21, first paragraph, lines 6-9), and

b) the locations of the hypervariable regions (i.e., CDRs1-3) are similar by either sequence (Kabat) or structural (Chothia) criterion, except for the first hypervariable loop of the heavy chain (or CDR1) (Winter et al, US 6,548,640B1, column 21, first paragraph, lines).

B. The limitation "antigen **binding affinity** similar to that of the donor immunoglobulin (the instant claim 29), or an affinity constant of at least $10^8\ M^{-1}$ (the instant claim 24), or in the range 10^8-$10^{12}\ M^{-1}$ (the instant claim 26)".

Queen et al teach, as an example, humanizing an immunoglobulin specific for IL-2 receptor (anti-Tac), which has a binding affinity of at least about $10^8\ M^{-1}$, and preferably $10^9\ M^{-1}$ to $10^{10}\ M^{-1}$ or stronger (Queen et al, 07/290,975, item under Summary, on page 4, and p.8 first paragraph). Queen et al also teach that the anti-Tac and the humanized anti-Tac have approximately the same affinity (Queen et al, 07/290,975, p.26, last paragraph, bridging p.27).

The binding affinity of the humanized immunoglobulin taught by Queen et al is clearly within the range of the claimed binding affinity. Further, the humanized immunoglobulin taught by Queen et al also has a binding affinity similar to that of the donor immunoglobulin.

C. The limitation "the antigen is an **IL-2** receptor (claim 26), or the donor immunoglobulin is the **anti-CD4** T-cell receptor antibody (claim 27), or the **anti-CD3** T-cell receptor antibody (claims 30-31).

Queen et al teach, as an example, humanizing an immunoglobulin specific for IL-2 receptor (anti-Tac), which has a binding affinity of at least about $10^8\ M^{-1}$, and preferably $10^9\ M^{-1}$ to $10^{10}\ M^{-1}$ or stronger (Queen et al, 07/290,975, item under Summary, on page 4, and p.8 first

paragraph). Queen et al also teach that the humanizing method can be used in combination with or to humanize monoclonal antibodies reactive with other markers on cells responsible for diseases, such as T cell markers in the group of "clusters of differentiation", as named by the first International Leukocyte differentiation workshop, Leukocyte typing, 1984, **which is incorporated herein by reference** (Queen et al, 07/290,975, page 15, last paragraph, bridging p.16, Queen et al, 07/310,252, page 18, last paragraph, bridging page 19).

The humanized immunoglobulin taught by Queen et al (07/290,975 and 07/310,252) clearly encompasses an immunoglobulin that binds to antigen IL-2 receptor (see for example Queen et al, 07/290,975, item under Summary, on page 4, and p.8 first paragraph), or an immunoglobulin that binds to an antigen, which antigen is CD-4 T-cell receptor or CD3 T- cell receptor, as evidenced by Lohmeyer J et al, 1987, Blut, 54(4): 223-9. Lohmeyer J et al teach a large panel of monoclonal antibodies corresponding to the clusters of differentiation antigens established on the Leukocyte typing Workshop I and II reveals unique T-cell phenotype, which antigens include CD3 and CD4 (abstract).

Thus all the limitations of the claims 24-31 of the instant application are met by the teaching of Queen patent US 5,585,089, which teaching is supported in the teaching of Queen et al, 07/290,975 and 07/310,252.

(10) Response to Argument

A. On pages 8-9, the response asserts that the reopening of the Office action of 05/02/2005 is not appropriate. The response asserts that the newly recited references in the

Office action of 05/02/2005 are cumulative, because they are also presented or incorporated by reference in Queen et al. The response asserts that the application has been pending for over eight years and includes seven Office action. The response asserts that the Office appears to be facilitating the further protraction of prosecution.

The arguments are not found to be persuasive. The reopening of the Office action of 05/02/2005 was appropriate and necessary, to change the rejection from the rejection under 35 USC 102(e) to the rejection under 35 USC 102(e)/103 over Queen et al, and to expand the reasons for rejection under 35 USC 102(e)/103. Further, the Winter reference was cited in the Office action to evidence that the claimed structural loop CDRs is the same as Chothia CDRs. The Lohmeyer reference was cited to evidence that the T cell antigens in the Leukocyte typing Workshop I and II, as referred to by Queen et al, include CD3 and CD4.

Regardless, the issue remains the same, i.e. whether the claimed invention is anticipated or in the alternative, as being obvious over the Queen patent US 5,585,098.

B. On page 9, Appellant requests that the evidence appendices, as cited in the previous Appeal brief filed on February 14, 2005, not to be resubmitted in the present Appeal brief, considering that there are over 250 pages of appendices.

In view that there are over 250 pages of appendices, the present Appeal brief is accepted and entered. The content of the appendices has been reviewed using the appendices of the previous Appeal brief filed on February 14, 2005.

C. Claims 24-31 are anticipated by, or in the alternative, obvious over Queen et al.

On pages 9-15, the response asserts that Appellants are attempting to provoke an interference with the Queen patent US 5,585,098, and that claims 24-31 are free of prior art, because the Queen patent US 5,585,098 is not an appropriate reference. The response asserts that US 5,585,098 is not entitled to the priority date of its two earliest priority application, 07/290,975 filed on December 28, 1988 and 07/310252 filed on February 13, 1989, because the claims in US 5,585,098 lack written description of: 1) "an affinity constant of at least 107 M-l," 2) "no greater than about four-fold that of the donor immunoglobulin;" and 3) "outside the Kabat and Chothia CDRs." The response asserts that not addressing the limitation of (1) and (2) in previous Office action reflects a misunderstanding of Appellant's arguments and of the law.

The arguments have been considered but are not found to be persuasive for the following reasons. The limitations in items 1 and 2 are not germane to the instant claims, because said limitations are not found in the instant claims. Further, the issue of whether the Queen patent US 5,585,098 per se is not entitled to earlier priority dates, i.e. whether the Queen patent US 5,585,098 is valid, is not an issue here, nor is it for the Examiner to decide.

Therefore, only arguments related to support for the limitation "outside of the Kabat and Chothia CDRs" in Queen prior applications, 07/290,975 filed on December 28, 1988 and 07/310252 filed on February 13, 1989, are addressed here (see below).

On pages 15-17, 22, the response discusses the prosecution of one of Queen's application, 07/634278, now patented, US 5,530,101, with Queen's amendment to obviate Riechman reference in an obviousness rejection. The response asserts that when faced with a

rejection over Riechman, Queen did not argue that CDR means Kabat plus Chothia.The response asserts that the limitation of "outside of the Kabat and Chothia CDRs" was simply added in a preliminary amendement that accompanied the filing of the application, which was issued as the Queen patent US 5,530,101. The response asserts that the amendment was necessary to secure allowance of the Queen patent claims over the prior art and is not supported by the parent applications.

The arguments have been considered but are not found to be persuasive for the following reasons. US 5,530,101, although also from Queen et al, is a different application than the instantly cited Queen patent US 5,585,089 as art in the instant application. The recitation of Queen's arguments in 07/634278, now patented, US 5,530,101, is not germane, because of the following reasons: 1) Each case is decided on its own facts. In other words, the decision on the application 07/634278, now US 5,530,101, e.g., how and why Queen's arguments overcome the obviousness by Riechman reference, is immaterial for the decision for the instant application. It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991), and 2) Further, the decision of whether there is support for the limitation "outside of the Kabat and Chothia CDRs" in Queen prior applications, 07/290,975 and 07/310252 is **based** mainly **on** the **content of the specification of 07/290,975 and 07/310252**, and not on Queen's arguments at a later date, and in another application.

On page 17, the response asserts that the two earliest priority applications did not require that there be changes to donor in the framework outside both the Kabat **and** Chothia CDRs. The response asserts that rather they describe a single change to donor anywhere in the framework,

including residues within the first Chothia heavy chain CDR (residues 26-32), or even, no change to donor in the framework. The response cites as example, both residues 27, and 30 to be changed are within the first Chothia CDR.

On pages 18-21, the response further asserts that the incorporation by reference by Kabat and Chothia are only in one passage on page 9, lines 1-5 in the 975 application. The response asserts that other passages specifically referring to CDRs make it clear that the CDRs are as defined by Kabat. The response asserts that the other passage referring to Chothia (p.13, lines 1-18 of the 252 application) is only in the context of computer program for computer modeling of antibodies. The response concludes that the interpretation of the term "CDRs" as found in the claims of the Queen patent US 5,585,089 is inconsistent with the claims, specification, and file history of the Queen patent US 5,530,101, much less, the two earliest priority documents. The response again asserts that the specification of Queen et al does not define the term CDRs as meaning Kabat and Chothia, but rather the specification defines CDRs in terms of Kabat, as shown in the general protocol set forth at column 14 of Queen patent (Category 1: The amino acid position is in a CDR is defined by Kabat).

The response has been considered but is not found to be persuasive for the following reasons. Contrary to the response assertions, the teaching in Queen et al, US 5,585,089, clearly has support in the prior applications of Queen et al, 07/290,975 and 08/310252 for the following reasons.

It is noted that the first hypervariable region, also called CDR1, as described by Kabat (amino acids 31-35), and Chothia (amino acids 26-32) is known in the art, and the description of

Kabat and Chothia CDRs is **incorporated by reference by Queen et al** (Queen et al, 07/290,975, p.8, last paragraph, bridging p.9, lines 1-5).

The humanized antibody taught by Queen et al, 07/290,975 or 07/310252, clearly comprises donor amino acids in the framework and outside of both Kabat and Chothia CDRs, and thus anticipates the claimed humanized antibody. For example, the following donor amino acids, taught in a specific example of an anti-Tac immunoglobulin disclosed by Queen et al, 07/290,975, are outside of both Kabat and Chothia CDRs:

1) Donor amino acids corresponding to amino acids of the human acceptor framework that are rare, such as amino acids 93, 107-109, 11 in the human framework of the anti-Tac immunoglobulin (Queen et al, 07/290975, p.21, item 2, lines 23-27, and Queen et al, 07/310252, p.21, item 2, lines 23-26),

2) Donor amino acids corresponding to the human framework amino acids that are immediately adjacent to one the CDRs, such as amino acid 67 in the human framework of the anti-Tac immunoglobulin (Queen et al, 07/290975, p.21, item 3, lines 28-30), and

3) Donor amino acids corresponding to the human framework amino acids that are physically close to the antigen binding region, as suggested by 3-dimensional modeling, such as amino acids 48, 68 in the human framework of the anti-Tac immunoglobulin (Queen et al, 07/290975, p.21, item 4, lines 31-34).

Thus, it is clear that many of the replaced amino acids in the framework of a humanized immunoglobulin, as taught by Queen et al, that belong to at least one of the following three categories: (I) adjacent to a CDR in the donor immunoglobulin sequence, or (II) capable of interacting with amino acids in the CDRs, or (III) rare at its position for human immunoglobulin

sequences (three categories in Queen et al, 07/310252, p. 10-13, and claim 4 of Queen et al, US 5,585,089), are "inherently" outside of both the CDRs as described by Kabat, "and" the structural loop CDRs as described by Chothia et al, wherein CDRs as described by Kabat and Chothia are known in the art, as incorporated in reference by Queen et al, *supra*.

In other words, the limitation of "a humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside the Kabat and Chothia CDRs that replace the corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, wherein each of these said donor amino acids:

(I) is adjacent to a CDR in the donor immunoglobulin sequence, or

(II) is capable of interacting with amino acids in the CDRs, or

(III) is typical at its position for human immunoglobulin sequences, and the replaced amino acid in the acceptor is rare at its position for human immunoglobulin sequences" as taught in claim 4 in Queen et al, US 5,585,089, clearly has support in the prior applications of Queen et al, 07/290,975 and 07/310, 252.

Further, contrary to the response assertion, there is **no limitation** in Queen et al that the CDRs **has to be** specifically Kabat CDRs when humanizing immunoglobulin. For example, in a general protocol teaching humanizing immunoglobulin by replacing the framework amino acid(s) that belongs to at least one of the following three categories: (I) adjacent to a CDR in the donor immunoglobulin sequence, or (II) capable of interacting with amino acids in the CDRs, or (III) rare at its position for human immunoglobulin sequences, only the generic term framework is referred to (Queen et al, 07/310,252, pages 10-13). Further, the teaching of Queen et al does

not limit that the framework has to be Kabat framework, in view of the incorporation by reference, by Queen et al, 07/290,975, of both Kabat and Chothia CDRs.

In addition, concerning the response assertion that the claims of the Queen patent US 5,585,089 is inconsistent with the claims, specification, and file history of the Queen patent US 5,530,101, Appellant is reminded that each case is decided on its own facts. It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991).

On pages 22-24, the response discusses the prosecution of Queen's European patent 451,216, reciting Queen's arguments.

The response is not found to be persuasive. The recitation of Queen's arguments in other Queen's applications is not germane, because each case is decided on its own facts. It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991).

On pages 25-28, the response asserts that that the Office changes position, when arguing that the Office means that CDRs as taught by Queen et al, could be interpreted as either Kabat **or** Chothia CDRs, rather than Kabat **and** Chothia CDRs. The response asserts that the first limitation of claim 1 of Queen patent US 5,585,089 does not recite Kabat or Chothia CDRs but merely CDRs. The response asserts that the specification does not define the term "CDRs" as meaning Kabat or Chothia. The response asserts that interpretation of CDRs of claim 1, as either Kabat or Chothia would make the claim indefinite, because the first Kabat CDR comprises residues 31-35, wherein the first Chothia CDR comprises residues 26-32, and the limitation will

change, depending on the limits of the CDRs. The response asserts that such interpretation also make the recitation "outside the Kabat and Chothia CDRs" of claim 1 superfluous. The response asserts the record of Queen's arguments in another Queen patent, US 5,530,01 does not support this latter interpretation of CDRs either, i.e. either Kabat or Chothia CDRs, because Queen did not argue that CDR means Kabat or Chothia.

The response is not found to be persuasive.

The Examiner did not change the position. The Examiner apologizes that the passage in the Office action of March 2003, page 4, is confusing to Applicant. As asserted in the Office action of August 2003, sentence bridging pages 3-4, and again in the following Office actions of 07/12/04 and 05/02/2005, the Examiner has clearly explained the Examiner's position, i.e. the Examiner meant that the term CDRs, **as incorporated by reference** by Queen et al in the 07/290975 application, could be interpreted as either Kabat or Chothia CDRs. It is noted that the hypervariable regions taught by Chothia et al are also called CDR's according to Queen et al (Queen et al, 07/290975 application, p. 8, last paragraph, bridging p.9).

Said interpretation does not make claim 1 of Queen US 5,585,089 indefinite, because in claim 1, the particular CDRs are recited, i.e., **both** Kabat and Chothia CDRs are referred to, based on the **defining** language "**wherein** said humanized immunoglobulin **comprises amino acids** from the donor immunoglobulin framework **outside** the Kabat **and** Chothia CDRs" in claim 1. In other words, it is clear to one of ordinary skill in the art which CDRs are referred to in claim 1, i.e. both of Kabat and Chothia CDRs in the humanized antibody taught by Queen et al.

Moreover, said limitation in claim 1 that the replacing donor amino acids in the framework comprises amino acids that are outside of the Kabat and Chothia CDRs is certainly supported by the prior applications 07/290,975 and 07/310,252 of Queen et al, as shown in the specific example of a humanized anti-Tac immunoglobulin, supra, and in the description of Kabat and Chothia CDRs, which is known in the art, and is incorporated by reference on pages 8-9 of Queen application 07/290,975,supra.

Concerning the assertion that the record of Queen's arguments in another Queen patent, US 5,530,01 does not support this latter interpretation of CDRs either, i.e. either Kabat or Chothia CDRs, Appellant is reminded that each case is decided on its own facts. It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991).

On pages 27-28, the response asserts that the Office's analysis focuses upon enablement, which is distinct from written description and definiteness. The response again asserts that there is however no support for the language "outside of the Kabat and Chothia CDRs" in the prior applications.

The response is not found to be persuasive.

Contrary to the response, all three criteria, written description, enablement and definiteness were discussed in the prior Office action. The language "comprising the donor amino acids outside of the Kabat and Chothia CDRs" of claim 1 of the Queen patent US 5,585,089 clearly meets the written description requirement, because it has support in the prior

applications 07/290,975 and 07/310,252 of Queen et al, as shown by the positions of the donor amino acids outside of the Kabat and Chothia CDRs cited in the specific example of a humanized anti-Tac immunoglobulin, supra, and by the description of Kabat and Chothia CDRs, which is incorporated by reference on pages 8-9 of Queen application 07/290,975, supra. Further, claim 1 is definite, because it is clear from claim 1 that both Kabat and Chothia CDRs are referred to in the immunoglobulin sequence, in view of the defining language "wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside the Kabat and Chothia CDRs" in claim 1, supra. Claim 1 also meets the enablement criteria, because it is routine in the art to determine which amino acids constitute the Kabat CDRs (amino acids 31-35) and which amino acids constitute the Chothia CDRs (amino acids 26-32) for use to make the humanized antibody taught by Queen et al.

On page 28, the response asserts that the Examiner's assertion that **many** of the replaced amino acids are "inherently" outside of both the Kabat and Chothia CDRs is a misapplication of inherency. The response asserts that **many** of the replaced residues are outside of the Kabat and Chothia CDRs are insufficient to support a limitation requiring that **all** of the replaced residues to be outside of the Kabat and Chothia CDRs. The response recites, as an example, residue 27, which is within the Chothia CDR1.

The response is not found to be persuasive.

Contrary to the response assertion, the inherency is appropriate, because the missing specific language "outside of the Kabat and Chothia CDRs" is present in the description of the amino acid positions of the replacing donor amino acids in the specific example of an anti-Tac immunoglobulin, taught by the Queen application 07/290,975, supra. Such meaning is clear to

one of ordinary skill in the art, when one compares the amino acid position of the replacing donor amino acids with that of Kabat (amino acids 31-35) and Chothia (amino acids 26-32) CDRs.

Although the Queen application 07/290,975 does not explicitly teach that the humanized immunoglobulin comprises replacing donor amino acids that are outside of the Kabat and Chothia CDRs, however, the claimed humanized immunoglobulin appear to be the same as the prior art humanized immunoglobulin. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Further, the limitation requiring that **all** of the replaced residues to be outside of the Kabat and Chothia CDRs is not in the claims 24-31 of the instant application, nor in the claim 1 of the Queen patent US 5,585,089. Thus, the response argues **limitation not in the claims**.

Conclusion

No claims are allowed. All the limitations of the instant claims 24-31 are met by the teaching of the Queen patent US 5,585,089, as evidenced by Winter et al (US 6,548,640B1) and Lohmeyer J et al, 1987, Blut, 54(4): 223-9, wherein said limitations are supported, i.e. described, in the Queen prior applications 07/290,975 and 07/310,252.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

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Patent Examiner

November 03, 2006

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